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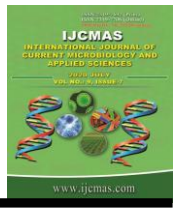

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Study on Chronic Rhinosinusitis: A Clinico-Mycological Perspective in a Tertiary Care Centre

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A B S T R A C T

Chronic Rhinosinusitis (CRS) is a group of multifactorial diseases characterised by inflammation of the mucosa of the nose and paranasal sinuses with a history of at least 12 weeks of persistent symptoms and signs despite maximal medical therapy. Fungi are being increasingly implicated in the etiopathology of chronic rhinosinusitis. Early diagnosis and accurate classification of fungal rhinosinusitis which depends on demonstration of fungus may help in directing appropriate anti-fungal therapy. Objectives: This study was undertaken to determine the prevalence of fungal agents involved in chronic rhinosinusitis (CRS) and to analyse its clinico-mycological profile. Fifty patients with clinical suspicion of CRS attending a tertiary care hospital during a 6 months period were included in this analysis. The sino-nasal specimens were collected from patients attending ENT department which included allergic mucin, mucopurulent exudate at sinus cavity, nasal exudate and tissue specimens collected by endoscopic sinus surgery; while a portion of surgically excised specimens were received in sterile normal saline, another part of the specimens in 10% formalin were sent to the histopathology laboratory. These were subjected to microscopy by KOH mount and fungal culture as per standard mycological technique. Tissue specimens were also subjected to histopathological examination for correlation and categorization of fungal rhinosinusitis (FRS). Male to female ratio was 1.27:1; age varied from 14 years to 64 years with majority of patients (66%) belonging to age group 21-40 years. The prevalence of FRS was 26%, and 76.9% of it was caused by *Aspergillus* spp. *Aspergillus flavus* (61.5%) was the most prevalent fungus isolated, followed by *Aspergillus niger* (15.3%), Mucor spp. (15.3%) and Curvularia spp. (7.6%) respectively. Non-invasive allergic fungal rhinosinusitis (AFRS) was the most common presentation (85%). FRS is a continuous spectrum of disease varying in presentation, treatment and long-term sequelae. Clinical suspicion of fungal sinusitis should be made in those patients presenting with CRS with the following signs and symptoms of nasal obstruction, discharge and polyps. Correct identification of the fungus remains essential for appropriate treatment.

Introduction

Rhinosinusitis is defined as the *inflammation* of nasal and paranasal sinus mucosa and is associated with *mucosal alterations* ranging from inflammatory thickening to gross nasal polyp formation.(1)

Rhinosinusitis (RS) is one of the most common health care problems across the world. There are evidences that show this disorder is increasing in prevalence and incidence. Approximately 20% of people experience this disease in their life. The most common form of RS is Chronic Rhinosinusitis (CRS). (2)

Chronic rhinosinusitis has a slow protracted course, and has different aetiologies, fungal infection being the major cause. Fungal organisms are one of the proposed aetiological agents and are seen in 6–12% of these patients. The subset of rhinosinusitis cases where the etiological role of fungi is proven or is considered to be important (due to its isolation from tissue biopsy samples) is referred to as Fungal Rhinosinusitis (FRS).(3)

The kingdom of fungi is ubiquitous and omnipresent. In general, numerous fungi of medical importance thrive as an indolent saprophyte or turn into a virulent invasive pathogen, depending on the host and environmental conditions.

Since the past two decades, fungi are increasingly recognized as a significant cause of morbidity and mortality among the patients (4) because of the wider use of broad-spectrum antibiotics, immunosuppressive therapy, cancer chemotherapy, increased incidence of immunodeficiency diseases and increased use of intensive care interventions.

Fungal colonization of the nose and paranasal sinuses appears to be a common finding in both normal and diseased states. Fungal rhinosinusitis (FRS) is increasing in prevalence; it causes significant physical symptoms, negatively affects quality of life and it can substantially impair daily functioning.

It presents in five clinicopathological forms, each with distinct diagnostic criteria, treatment and prognosis. The invasive forms are acute fulminant, chronic and granulomatous invasive fungal rhinosinusitis (IFRS). The non-invasive forms are fungal ball and allergic fungal rhinosinusitis (AFRS).

Early diagnosis and accurate classification of fungal rhinosinusitis which depends on demonstration of fungus may help in deciding the treatment protocol and preventing multiple surgical procedures, and may lead to effective treatment. Despite advances in medical and surgical treatment, it remains a major health burden and, in many cases, it is extremely challenging to treat.

Hence, this study was undertaken to determine the prevalence of fungal agents involved in chronic rhinosinusitis (CRS) and to correlate it with the various clinical presentations.

Materials and Methods

The study was planned as a prospective observational study. Fifty patients with clinical suspicion of CRS attending ENT OPD in Vijayanagara Institute of Medical Sciences, Ballari from January 2019 to December 2019 were included in the study, agreed by verbal consent to participate inthe study. Data was included in a predesigned format. It included patient's identification number, name, age, sex, patient's history, clinical presentation, radiological findings, microbiological results and histopathological diagnosis. Clinical assessment was done.

Samples collected were allergic mucin, mucopurulent exudate at sinus cavity, nasal exudate and tissue specimens collected by endoscopic sinus surgery. A portion of surgically excised specimens was received in sterile normal saline from mycology laboratory and another part of the specimens was received in 10% formalin in the histopathology laboratory.

The tissue specimens received at mycology laboratory were minced. Direct 10% KOH mount examination was performed for all these tissue specimens.

Histopathological examination of the specimens was done by haematoxylin and eosin and periodic acid-schiff stain (Figure 2).

Irrespective of direct KOH positivity, the specimens were subjected to fungal culture. According to the standard mycological practice, the specimens were inoculated into two sets of Sabouraud's Dextrose Agar (SDA), in duplicates, one set with gentamicin and cycloheximide and another set without cycloheximide. One set was incubated at 37°C and another set at 25°C for 30 days.(5)

In culture-positive samples, the isolate was identified by detailed macroscopic morphology of colonies and microscopic morphology by performing lactophenol cotton blue tease mount and slide culture technique.

Results of fungal cultures were reviewed and correlated with clinical and histopathological findings. A clinic-mycological approach was taken in arriving at a final diagnosis and categorization of FRS.

Results and Discussion

Age of the patients varied from 14 years to 64 years. Majority of patients (66%) belonged to an age group 21-40 years, and male to female ratio was 1.27:1.

All the patients presented with symptoms of nasal obstruction and nasal discharge, followed by headache and facial fullness in 82% and 64% of patients, respectively. KOH smear positivity in this study was 30% (Figure 1). Out of the 50sino-nasal specimens, 13 (26%) were culture-positive for fungus.

On the basis of histopathological findings, 12 cases were found to be of non-invasive fungal rhinosinusitis. These included 9 cases of allergic fungal rhinosinusitis, and 3 cases of fungal ball.1 case was of chronic invasive fungal rhinosinusitis type.

The distribution of isolated fungi from specimens of clinically diagnosed FRS patients is given in Table 1.

The prevalence of FRS was 26%, and 76.9% of which was caused by *Aspergillus spp. Aspergillus flavus* (61.5%) was the most prevalent fungus isolated, followed by *Aspergillus niger*(15.3%), *Mucor spp.* (15.3%) and *Curvularia spp.* (7.6%) respectively.(Figure 3, 4).

Out of 9 cases of AFRS, *Aspergillus flavus* (*A. flavus*) was the most common fungus isolated (five cases). In fungal ball, *A. flavus* was isolated in two cases and *Aspergillus niger* (*A. niger*) was isolated in one case.

Table.1 Distribution of fungal isolates identified among cases of fungal rhinosinusitis along with their histological classification.

Isolate	Invasive FRS	Non-invasive FRS		Total
		AFRS	Fungal ball	n (%)
Aspergillus flavus	1	5	2	8 (61.5%)
Aspergillus niger	-	1	1	2 (15.3%)
Mucor spp.	-	2	-	2 (15.3%)
Curvularia spp.	-	1	-	1 (7.6%)
				N = 13

Figure.1 Fungal elements in 10% KOH (400 X)

Figure.2 Fungalhyphae in H&E (1000X)

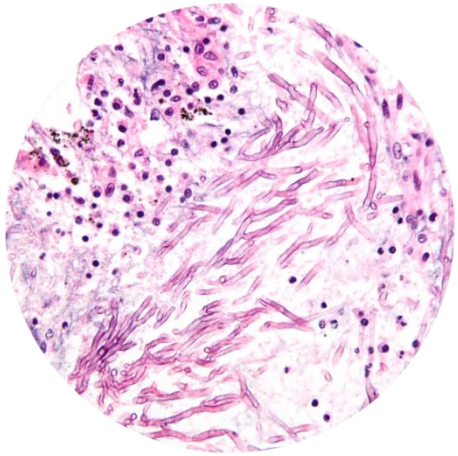

Figure.3 LPCB mount *Aspergillus flavus*

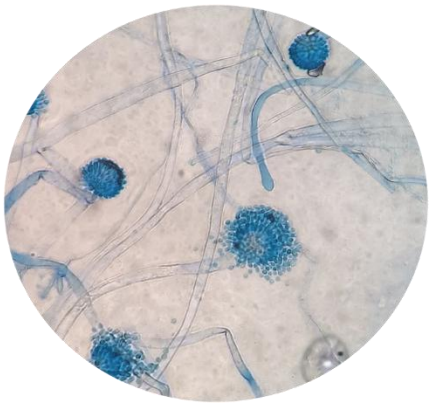

Figure.4 LPCB mount *Curvularia spp.*

Rhinosinusitis is defined as the inflammation of nasal and paranasal sinus mucosa, and it is a common disorder affecting approximately 20% of the population at sometime of their lives.(6) The prevalence is even greater in tropical countries like India.

CRS is characterised by sinonasal mucosal inflammation with a history of atleast 12 weeks of persistent symptoms and signs despite maximal medical therapy.(7)

There is emerging evidence that fungi play an important role in exacerbation and perpetuation of mucosal inflammation in CRS, and only in more recent times has the categorization of FRS been more fully defined.

A significant number of patients diagnosed with CRS often tend to have a final diagnosis of fungal rhinosinusitis. In a study by Chakrabarti *et al*., 56% fungal smear positivity has been reported (8); 30% KOH smear positivity was reported in this study.

Some studies have reported 10% and 40% prevalence of sino-nasal mycotic infections.(9,10) In the present study, the prevalence of fungal rhinosinusitis by fungal culture was 26% among patients with CRS. This correlates well with a study by Das *et al*., which reported 28.7% of fungal rhinosinusitis of all 665 cases of CRS over a period of five years.(11) In an another five-year study from south India, there were 63 biopsies diagnosed as FRS (31.7%) out of 138 biopsies of CRS in the study period.(12)

Seventy-seven percent of fungal rhinosinusitis was caused by *Aspergillus* sp., and *A. flavus* (61.5%) was the most common isolate, a finding that is supported by a study from Iran(7) and by various studies from other parts of India.(6,13) In a similar study by S. Prateek *et al*., *Aspergillus* sp. (76.19%) was the most common isolated species and *A. flavus* (57.14%) being the most common fungal isolate among all cases of fungal rhinosinusitis (14).

Aspergillus sp. is a chronic colonizer of paranasalsinuses and ears as well as associated with a variety of different clinical conditions.(15)

From most-invasive to least-invasive, these infections are classified into IFRS, AFRS and fungal ball.(13) The clinical presentations are also usually characteristic of each type.

Various studies have reported AFRS as the

most common form of fungal rhinosinusitis and it is more commonly seen in tropical climates such as that seen in India.(11,16) In a seven-year study, 63% had AFRS among 211 patients, with 24% and 10% presenting with acute and chronic invasive sinusitis, respectively. (17) In this study, 69.2% of fungal rhinosinusitis patients presented as AFRS, and 23.1% of patients presented as sinus fungal ball; 7% of CRS were categorized as IFRS.

AFRS patients are frequently atopic individuals clinically presenting as pansinusitis and nasal polyposis, (18) which is due to the allergic response to the fungus colonizing the mucin in their sino-nasal cavities.(19)

Patients with sinus fungal ball often clinically present as unilateral nasal obstruction, nasal polyp and discharge and is caused by the overgrowth of fungus in the nose and paranasal sinuses without an eosinophilic inflammatory reaction.(19)

Demonstration of fungal hyphae with characteristic cellular response or fungal culture positivity in properly collected sinus content in an otherwise characteristic patient is an important diagnostic criterion in these conditions.(18)

IFRS patients presented with diagnostic and therapeutic challenges. The histopathology of surgical sinus specimen played a major role in categorizing the IFRS patients.

Chronic granulomatous FRS is exclusively a histopathological diagnosis in which granulomatous response is seen with considerable fibrosis. It is primarily caused by *Aspergillus* sp. and is mainly located in Africa and Southeast Asia.(13)

In this study, an immunocompetent adult male chronic FRS patient presented with signs and symptoms of bony erosion involving osteomyelitis of left maxilla with unilateral proptosis. Histopathology showed non-caseating granulomas in the involved bone and tissue and *A. flavus* was isolated in culture.

For the chronic IFRS patient who clinically presented as nasal obstruction with proptosis *A. flavus* was isolated from tissue biopsy specimen.

Various authors propose fungal rhinosinusitis to be a continuous spectrum of disease starting from the non-invasive to the acute invasive varieties with considerable overlap and transition from one form to another in the same patient.(11)

Therefore, continuous surveillance of prevalent sino-nasal fungal infection and periodical monitoring of changing disease pattern of FRS patients are essential. A multi-disciplinary approach involving surgery and medical department with appropriate anti-fungals and immunotherapy is more successful in treating these patients.(20)

In conclusion, CRS not responding to standard therapy should be investigated for FRS.

Mycological identification plays a crucial role in diagnosing and categorizing CRS. It also provides therapeutic guidance for the other specialities, principally in the case of atypical presentation and in infection with less common agents.

As each of the clinicopathological variants of FRS is associated with unique geographical and host-related risk factors and different etiological agents, knowledge of the prevalent fungal agents is important. Hence, a regular

monitoring of fungal infections is required to study the prevalent pattern and monitor the emerging pattern of these infections.

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